An Open-Label, Three-Part, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor GSK1120212, BRAF Inhibitor GSK2118436 and the anti-EGFR Antibody Panitumumab in Combination in Subjects with BRAF-mutation V600E Positive Colorectal Cancer.

Published: 12-04-2013
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Part 1 primary objectives: To determine the safety, tolerability and range of tolerated combination doses in subjects with BRAF-V600E mutation-positive CRC intwo dosing groups:* dabrafenib dosed orally in combination with panitumumab * trametinib...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON47621

Source
ToetsingOnline

Brief title
MEK116833

Condition

- Other condition
- Gastrointestinal neoplasms malignant and unspecified

Synonym
colorectal cancer

Health condition

Colorectal Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: GlaxoSmithKline group of companies

Intervention

Keyword: colorectal cancer

Outcome measures

Primary outcome

Part 1 primary objectives:

To determine the safety, tolerability and range of tolerated combination doses

in subjects with BRAF-V600E mutation-positive CRC in

two dosing groups:

* dabrafenib dosed orally in combination with panitumumab

* trametinib dosed orally in combination with dabrafenib and panitumumab

Part 2 primary objectives:

To determine the safety, tolerability and range of tolerated combination doses

in subjects with BRAF-V600E mutation-positive CRC in

two dosing groups:

* dabrafenib dosed orally in combination with panitumumab

* trametinib dosed orally in combination with dabrafenib and panitumumab

Secondary outcome

Part 1 secondary objectives:

To describe the pharmacokinetics of dabrafenib, trametinib and panitumumab

after combination therapy

To determine preliminary clinical activity of dabrafenib dosed orally in

combination with panitumumab

To determine clinical activity of trametinib dosed orally in combination with

dabrafenib and panitumumab

Part 2 secondary objectives:

To characterize the population PK parameters of dabrafenib and trametinib dosed

orally in combination with anti-EGFR antibody (panitumumab)

To characterize the durability of response with dabrafenib dosed orally in

combination with panitumumab

To characterize the durability of response with trametinib dosed orally in

combination with dabrafenib and panitumumab

Study description

Background summary

The study is designed to identify the recommended Phase 2 dose/regimen for the doublet (dabrafenib/panitumumab) and the triplet (dabrafenib/trametinib/panitumumab) in Part 1, identify an initial signal of clinical activity in Part 2 and to perform a randomized comparison of the experimental arms to a chemotherapy comparator arm (a regimen of FOLFOX or FOLFIRI with or without panitumumab or bevacizumab) in Part 3. Extrapolating from the experience in BRAF V600E -mutation positive melanoma, it is expected that the triple combination is likely to provide the greatest benefit to subjects, in which case the inclusion of the double combination serves as a control to assess the important *contribution of components* question. However, another possible outcome is that the double combination is superior (e.g., due to poor tolerability of the triple combination), an outcome that this study design will also adequately evaluate.

Study objective

Part 1 primary objectives:
To determine the safety, tolerability and range of tolerated combination doses in subjects with BRAF-V600E mutation-positive CRC in two dosing groups:
* dabrafenib dosed orally in combination with panitumumab
* trametinib dosed orally in combination with dabrafenib and panitumumab

Part 2 primary objectives:
To determine the safety, tolerability and range of tolerated combination doses in subjects with BRAF-V600E mutation-positive CRC in two dosing groups:
* dabrafenib dosed orally in combination with panitumumab
* trametinib dosed orally in combination with dabrafenib and panitumumab

Study design

This study will evaluate the safety, tolerability and efficacy of the doublet dabrafenib/panitumumab and triplet trametinib/dabrafenib/panitumumab combinations in subjects with BRAF- mutation V600E positive CRC. Part 1 includes a 3+3 dose escalation that will identify tolerable combination doses for the two combinations. The safety and tolerability of these combination doses will be confirmed in expansion cohorts in Part 2, followed by a randomized evaluation of the efficacy and safety of the combinations in Part 3.

Intervention

Patients will be enrolled in two dosing groups:

* dabrafenib in combination with panitumumab
* trametinib in combination with dabrafenib and panitumumab

Study burden and risks

See C4.

Contacts

Public
Novartis

Lichtstr. 35
Basel 4056
CH
Scientific
Novartis

Lichtstr. 35
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CH

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* BRAF V600E mutation positive colorectal cancer (CRC), as determined by local genetic testing.
* Provision of archival tissue; if archival tissue is not available or found to not contain tumor

tissue, a fresh biopsy is required.
* Willingness to follow contraception requirements.
* ECOG 0 or 1.
* LVEF *LLN, or 50% if not defined by institution.
* Organ function as noted in Table 17:
* ANC *1.2 × 109/L
* Hemoglobin *9 g/dL or 5.6 mmol/L
* Platelets *75 × 109/L
* PT/INR and PTT *1.5 x ULN
* Mg++ * LLN
* Albumin *2.5 g/dL or 25 g/L
* Total bilirubin *1.5 x ULN
* Creatinine * 1.5 ULN or Calculated creatinine clearance * 50 mL/min

Exclusion criteria

* Prior malignancy, other than colorectal cancer.
* Prior exposure to BRAF or MEK inhibitors.
* Part 2 ONLY* prior exposure to EGFR antibodies or inhibitors.
* KRAS mutation positive.
* Received an investigational or approved anti-cancer drug within 4 weeks, or within 5 half-lives (whichever is shorter) of the first dose of study drug(s). At least 14 days must have passed between the last dose of prior investigational agent and the first dose of study drug(s).
* RVO, CSR or predisposing factors to RVO or CSR. Ophthalmic exam is required at screening, and intraocular pressure must not exceed 21mm Hg.
* Brain mets must be stable *90 days and treated with surgery or stereotactic radiosurgery.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped

Start date (anticipated):	18-09-2013
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dabrafenib
Generic name:	Dabrafenib
Product type:	Medicine
Brand name:	Trametinib
Generic name:	Trametinib
Product type:	Medicine
Brand name:	Vectibix
Generic name:	panitumumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-04-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-07-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	27-09-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	16-01-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-04-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-11-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	29-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	01-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	23-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-03-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-04-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	

Date:	27-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-08-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	08-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-004802-81-NL
ClinicalTrials.gov	NCT#01750918

Register	ID
CCMO	NL43976.031.13